REMARKS

Amendments are presented herein to improve the form of the subject application and in response to the Examiner's comments in the above-identified Office Action.

Status of the Claims

Claims 1-10 are in the case.

Objections to the Disclosure

The disclosure is objected to because of an informality at page 5, line 5. According to the Examiner, there is no antecedent for the definition.

Page 5, line 5 has been amended to clearly indicate that the solid and dashed lines ("----") shown on Formula I between carbons 5 and 6 and carbons 13 and 14 "represent any combination of a single bond or a *cis* or *trans* double bond." This does not constitute new matter since Formula I clearly shows the solid and dashed lines. The normal convention for a double bond would be two solid lines.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-6 stand rejected as being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant is instructed to see the objection to the text of the specification (*vide infra*).

Independent claims 1 and 6 have been amended, as indicated hereinabove, to clearly indicate that the solid and dashed lines ("----") shown on Formula I between carbons 5 and 6 and carbons 13 and 14 "represent(s) any combination of a single bond or a *cis* or *trans* double bond." Although not

specifically referenced in this rejection, independent claim 8 also suffers from the same inadvertent typographical error as independent claims 1 and 6. Therefore, Applicant has similarly amended claim 8.

In view of the foregoing, it is respectfully asserted that Examiner's rejections to independent claims 1, 6, and 8, and hence dependent claims 2-5 and 9, have been overcome by the amendments presented herein.

Inasmuch as claim 6 is not subject to rejection based on prior art, it is believed that claim 6 is now in allowable form.

Rejections Under 35 U.S.C. § 102(b)

Claims 1 and 3-5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,045,449 issued on August 30, 1977 to Bundy (hereinafter "Bundy").

Applicant's attention is directed to Bundy at Examples B-4, B-3 and 51 which, according to the Examiner, teach claims 3-5, respectively.

Bundy teaches a plurality of 1,15 lactones of prostaglandin-type free acids, including PGF-type prostaglandins, and alleges that these lactones would be useful for the same pharmacological purposes as the corresponding prostaglandin-type free acids.

Nevertheless, Bundy does teach 1,15-lactones of $PGF_{2\alpha}$ analogs where, using Applicant's terminology, R_9 and R_{11} are both H so that the substituents on the cyclic ring are hydroxyls (-OH). See, for example, the broad formula in Bundy for 1,15-lactones at Col. 62, lines 3-40; Col. 12, lines 25-45; Col. 23, line 55-Col. 24, line 11 and the compounds in Table B beginning at Cols. 103-104.

However, Bundy nowhere teaches or suggests that the ring hydroxyls of the PGF analogs can be derivatized as an alkyl ester. In other words, Bundy nowhere teaches or suggests embodiments where one or both R_9 and R_{11} are C1-20 alkyls. Therefore, any compound according to Applicant's independent claim 1 where one, or both, R_9 and R_{11} are C1-20 alkyls are not taught or suggested by Bundy.

In the compounds most closely related to the compounds claimed by Applicant, specifically 1,15-lactones of $PGF_{2\alpha}$ analogs, Bundy does teach embodiments where R_9 and R_{11} are both H and the $PGF_{2\alpha}$ analog structure at positions 2-6 in the alpha chain is defined at Col. 13, lines 33-39 as Z_1, illustratively, Z_1 = -CH=CH-CH_2-CH_2-CH_2- or -CH=CH-CH_2-CH_2-CF_2-. Thus, in Applicant's terminology, Bundy teaches that X = -CH_2 and R_1 and R_2 are the same and are either -H or -F. In fact, Bundy nowhere teaches that the X moiety can be anything other than methylene. Thus, Bundy nowhere teaches or suggests Applicant's embodiments where X = -O, -S, or -NH. Nor does Bundy teach or suggest any embodiments where R_1 and R_2 are -CH_3.

Further, in these same $PGF_{2\alpha}$ analogs, Bundy teaches that the substituent at position 17 on the omega chain, defined at Col. 13, lines 14-29, as R_7, can be a substituted or unsubstituted phenyl or phenoxy. Substituents on the phenyl ring, defined by Bundy at Col. 13, lines 23-26 as $(T)_s$ are chloro, fluoro, trifluoromethyl, alkyl or alkoxy of one to 3 carbon atoms, inclusive, where s = 0-3. In Applicant's terminology, this means that Y = -CH_2- or - O - and that Z = -H, -Cl, -F, -CF_3, C_1-C_3 alkyl or C_1-C_3 alkoxy. Bundy nowhere teaches or suggests embodiments where Y is -S or -NH. Nor

does Bundy teach or suggest any embodiments where Z is -Br,-I, or straight chain or branched alkyls having more than 3 carbon atoms.

In summary, any compounds according to Applicant's independent claim 1 where one, or both, R_9 and R_{11} are C1-20 alkyls are not taught or suggested by Bundy. However, in compounds where both R_9 and R_{11} are H, X can not be $-CH_2-$ when Y is -O- or $-CH_2-$ unless R_1 and R_2 are selected to be $-CH_3$, or Z is selected to be -Br, -I, or a C_4-C_{10} straight chain or branched alkyl. In view of the foregoing, Applicant has amended independent claim 1 to include the following proviso: "when $R_9 = R_{11} = H$, X is O, S, or NH if Y is O or CH_2 unless R_1 and R_2 are selected to be CH_3 or Z is selected to be Br, I, or a C_4-C_{10} straight chain or branched alkyl." It is respectfully asserted that this amendment clearly overcomes the Examiner's rejection under 35 U.S.C. § 102.

Claims 3-5, are dependent on claim 1, and therefore include all of the limitations of claim 1, including the new proviso. As applied to claims 3-5, the proviso prevents both R_9 and R_{11} from being H, since X is $-CH_2-$ and Y is -O-, -O-, and $-CH_2-$, respectively. Therefore, it is believed that rejections of claims 3-5 under 35 U.S.C. § 102 have also been overcome.

Inventorship

The Examiner states that this application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants acknowledge that they have been advised by the Examiner of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim

that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Based on information and belief, inventors Maxey and Stanton were both obligated to assign the invention to the assignee hereof at the time the invention was made.

Rejections Under 35 U.S.C. § 103

Claims 1 and 2 stand rejected under 35 U.S.C. § 103(a) as specifying obvious subject matter over Bundy. According to the Examiner, claims 1 and 2 are generically taught. The instant compound differs from Ex. 53 solely in the Z group which is methyl instead of H. On page [sic]13, line 23, Bundy teaches that this moiety, T in Bundy, may be H or lower alkyl rendering the instant compound structurally and patentably obvious.

Referring to Bundy at Col. 88, beginning at line 52, Ex. 53 is stated to be 16-phenoxy, 17, 18, 19, 20-tetratranor-$PGF_{2\alpha}$ 1,5-lactone [sic]. However, the reader is referred to Formula XXII, which is found at Col. 26, lines 45-55, and is a 1,9-lactone. Nevertheless, assuming that Ex. 53 refers to a 1,15-lactone, Ex. 53 teaches an embodiment where $R_9 = R_{11} = H$, X is $-CH_2-$, Y = -O-, and R_1 and R_2 are -H, and Z is -H.

Independent claim 1, as amended, excludes compounds where X is $-CH_2-$, if $R_9 = R_{11} = H$ and if Y is -O- unless R_1 and R_2 are selected to be $-CH_3$ or Z is selected to be -Br, -I, or a C_4-C_{10} straight chain or branched alkyl. Therefore, claim 1, and consequently dependent claim 2, would be limited to compounds where X is selected from -O, -S, or -NH. For reasons set forth hereinabove, Bundy

neither teaches or suggests embodiments where X is O, S, or NH irrespective of the moieties at R_1, R_2, R_9, R_{11}, Y, and Z.

Moreover, Bundy nowhere teaches or suggests embodiments where one or both R_9 and R_{11} are C1-20 alkyls. Esters have increased lipophilicity, and hence, increased activity as an ophthalmic prodrug and an increased ability to be absorbed by the cornea. In fact, Bundy does not even contemplate ophthalmic uses for the 1,15-lactones of $PGF_{2\alpha}$ analogs disclosed therein (see, Col. 64, lines 23-58). Therefore, Bundy neither teaches nor suggest any of Applicant's claimed compounds wherein either R_9 or R_{11}, or both, are not H irrespective of the moieties at R_1, R_2, X, Y, and Z.

Further, Bundy neither teaches nor suggests any embodiments where Y is S or NH irrespective of the moieties at R_1, R_2, R_9, R_{11}, X, and Z. Likewise, Nor does Bundy teach or suggest any embodiments where Z is Br, I, or straight chain or branched alkyls having more than 3 carbon atoms or R_1 and R_2 are $-CH_3$.

In conclusion, it is respectfully asserted that independent claim 1, as amended, is neither taught nor suggested by Bundy. Claim 2, dependent thereon, is likewise neither taught nor suggested by Bundy.

Allowable Subject Matter

Claims 7-10 have been allowed.

In view of the foregoing, it is respectfully requested that the Examiner reconsider the present application, allow the claims, and pass the application for issue. If the Examiner believes that the

prosecution of this case can be expedited by a telephone interview, the Examiner is requested to call attorney for Applicant(s) at the telephone number indicated hereinbelow.

Respectfully submitted,

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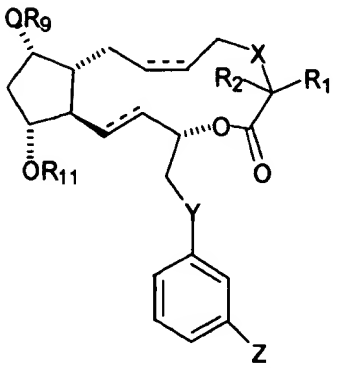
BJR:rk:roa.cm2
enc. - Annexures 1 and 2

Annexure 1 - Claims Rewritten to Show Amendments

1. (Amended) A compound of the general formula:



Formula I

wherein X is O, S, NH or CH_2;

R_1 and R_2 are the same and are either H, CH_3 or F;

R_9 is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

R_{11} is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

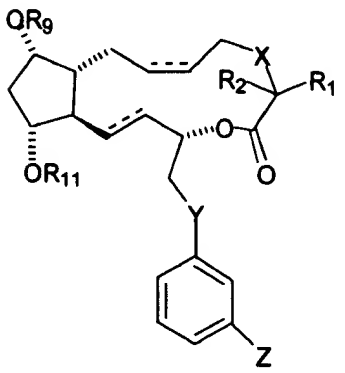
---- represents any combination of a single bond, or a [cis] *cis* or [trans] *trans* double bond;

Z is H, Cl, Br, I, CF_3, CH_3, or C_1-C_{10} straight chain or branched alkyl; and

Y is O, S, NH or CH_2 provided that when $R_9 = R_{11} = H$, X is O, S, or NH if Y is O or CH_2 unless R_1 and R_2 are selected to be CH_3 or Z is selected to be Br, I, or a C_4-C_{10} straight chain or branched alkyl.

6. (Amended) A method of treating increased intraocular pressure in the eye of a human or animal comprising the step of:

administering a therapeutically effective amount of at least one compound of the general formula to the eye:



Formula I

wherein X is O, S, NH or CH_2;

R_1 and R_2 are the same and are either H, CH_3 or F;

R_9 is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

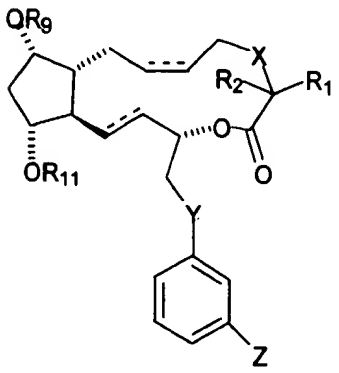
R_{11} is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

---- represents any combination of a single bond, or a [cis] *cis* or [trans] *trans* double bond;

Z is H, Cl, Br, I, CF_3, CH_3, or C_1-C_{10} straight chain or branched alkyl; and

Y is O, S, NH or CH_2.

8.(Amended) A topical ophthalmic composition for treating increased intraocular pressure comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one compound of the general formula:



Formula I

wherein X is O, S, NH or CH_2;

R_1 and R_2 are the same and are either H, CH_3 or F;

R_9 is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

R_{11} is H, or C_1-C_{20} straight chain, saturated or unsaturated or branched acyl;

---- represents any combination of a single bond, or a [cis] *cis* or [trans] *trans* double bond;

Z is H, Cl, Br, I, CF_3, CH_3, or C_1-C_{10} straight chain or branched alkyl; and

Y is O, S, NH or CH_2.

Annexure 2 - Text Rewritten to Show Amendments

Amend page 5, the subparagraph at line 5 as follows:

the solid and dashed lines (----) [represents] represent any combination of a single bond, or a *cis* or *trans* double bond;